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Citation for published version:

Möttus, R, Luciano, M, Starr, JM & Deary, IJ 2013, 'Diabetes and life-long cognitive ability', *Journal of Psychosomatic Research*, vol. 75, no. 3, pp. 275-278. <https://doi.org/10.1016/j.jpsychores.2013.06.032>

Digital Object Identifier (DOI):

[10.1016/j.jpsychores.2013.06.032](https://doi.org/10.1016/j.jpsychores.2013.06.032)

Link:

[Link to publication record in Edinburgh Research Explorer](#)

Document Version:

Peer reviewed version

Published In:

Journal of Psychosomatic Research

Publisher Rights Statement:

© Möttus, R., Luciano, M., Starr, J. M., & Deary, I. J. (2013). Diabetes and life-long cognitive ability. *Journal of Psychosomatic Research*, 75(3), 275-278. [10.1016/j.jpsychores.2013.06.032](https://doi.org/10.1016/j.jpsychores.2013.06.032)

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Supplementary Data

Diabetes and life-long cognitive ability

René Möttus, Michelle Luciano, John M. Starr, and Ian J. Deary

1. The role of educational level in cognitive ability-diabetes association

Educational level was coded in five categories, ranging from 'no qualification' to 'degree'. Educational level was negatively associated with diabetes, such that each additional educational level incurred 26% lower odds of having self-reported diabetes (OR = 0.74, 95% CI: 0.60, 0.90) and 22% lower odds of having a HbA1C level above 6.5% (OR = 0.78, 95% CI: 0.66, 0.92).

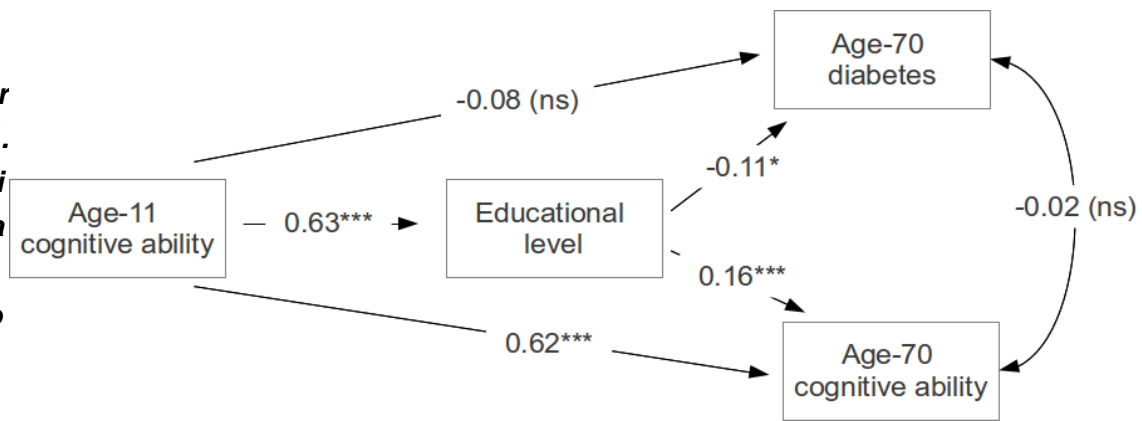
Next, we attempted to fit educational level in the life-course model of cognitive ability and diabetes. As has been discussed at length in an epidemiological setting, there are arguments for considering educational level as both the outcome and contributor to cognitive ability, such that higher initial cognitive ability level contributes to obtaining better education, which, then, further contributes to cognitive ability [1]. As a result, and given the time-line of events, it is probably the best to consider age-11 cognitive ability as a causal contributor to both educational level and age-70 cognitive ability, with the latter also being influenced by educational level. As for diabetes in older age, it is possible that it is linked to educational level (such as was described in the previous paragraph) but it also receives both direct and indirect (via educational level) contributions from childhood cognitive ability. The only real difficulty is related to the causality in the associations between older-age diabetes and cognitive ability: diabetes is typically considered to be causal to cognitive functioning but the findings of the present study (people with diabetes in older age had similarly lower cognitive ability already in childhood) seem to suggest the opposite. So, for the moment, it is probably best to remain agnostic about the causality in this association.

We tested these multivariate associations by means of structural equation modelling as implemented in the Mplus 6 software [2]. The specified model, which is based on the reasoning above and treated self-reported diabetes as a categorical variable, is shown in the Figure S1 along with standardized model estimates. The model used weighted least squares means and variance adjusted (WLSMV) estimation. Due to unclear causality in the association between older-age diabetes and cognitive ability, we specified this association as a correlation. Also, although not shown in the model, all variables were residualized for sex, whereas diabetes and age-70 cognitive ability were also residualized for age at the older-age testing. The model fit data acceptably well: comparative fit index (CFI) = 1.00, root mean square error of approximation (RMSEA) = 0.064 (90% confidence intervals: 0.019, 0.122).

Figure S1 shows that, after considering the contributions from childhood cognitive ability, educational level, only the latter made an independent significant contribution to diabetes status. However, two things should be emphasized.

First, educational level received a strong contribution from age-11 cognitive ability and, therefore, the latter was likely to indirectly (via education) contribute to diabetes status in older age. In other words, education was likely to mediate the childhood cognitive ability-older age diabetes association. A formal statistical test (in Mplus 6) confirmed this: the indirect effect of age-11 cognitive ability to diabetes was $\beta = -0.07$ ($p = 0.02$). As a result, the total effect was $\beta = -0.08 + (-0.07) = -0.15$ and it was statistically significant ($p = 0.007$).

Figure S1.
Multivariate associations between



een cognitive ability, educational level and diabetes as tested using structural equation modelling. The estimates are standardized coefficients. * $p < 0.05$; *** $p < 0.001$; ns = non-significant.

Second, in this multivariate model the association between age-70 cognitive ability and diabetes was close to zero, suggesting little causal role of diabetes on cognitive ability over and above the contributions of pre-existing cognitive ability and educational level.

Fairly similar results were obtained with HbA1C-based diabetes groupings.

2. Differences across diabetes medication groups

In principle, cognitive benefit may be achievable with pharmacological interventions targeting glycemic control in patients with type 2 diabetes [3]. As a result, medication status of the people with diabetes may have influenced the findings. Indeed, if medicines targeting glycemic control had raised cognitive ability, then the true older age cognitive ability difference between those with and without diabetes would have been larger than the difference that we observed, given that nearly half of the people with self-reported diabetes used non-insulin diabetes medication. This would have suggested that diabetes may have, after all, impaired general cognitive ability in this sample.

Since we had information on the medications that people used, we could test this. If medications targeting glycemic control had improved cognition, we would probably have seen that (a) those on non-insulin diabetes medications scored higher than those people with diabetes who did not use diabetes medications and (b) the pattern of *relative* cognitive ability levels at ages 11 and 70 was different in those people with diabetes who used non-insulin diabetes medications compared to the rest of people with diabetes. Table S1 gives the mean standardized cognitive ability test scores of participants on different types of or no diabetes medication.

Contrary to the hypotheses discussed above, Table S1 shows that people on non-insulin diabetes drugs had, in fact, lower cognitive ability than those people with diabetes who did not report taking any diabetes medications (the number of people on insulin was very low and therefore their mean cognitive ability levels are probably not reliable and interpretable). Furthermore, perhaps even more important is the finding that the relative cognitive ability test scores (z-scores) were similar in age 11 and 70 years in both of these groups (i.e., people on non-insulin diabetes drugs and people with diabetes who were not on diabetes medication). That is, although people on diabetes drugs tended to have lower cognitive test scores than those people with diabetes who attempted to manage their disease without drugs or did not manage it at all, the cognitive ability difference had been there already at age 11. As a result, based on these data, it is not likely that using a certain

type of medicine biased diabetes-related cognitive ability differences in old age relative to the differences in childhood.

Table S1. Standardized cognitive ability test scores of people on different types of diabetes medication or no diabetes medication.

	Age 11 cognitive ability			Age 70 cognitive ability	
	N	Mean	SD	Mean	SD
<i>Self-reported diabetes</i>					
Diabetes, on insulin	11	-0.44	0.55	-0.06	0.72
Diabetes, on other diabetes drug	41	-0.55	1.22	-0.60	1.21
Diabetes, no drug	33	0.01	1.04	0.01	1.12
No diabetes	932	0.03	0.99	0.03	0.98
<i>HbA1C-based diabetes</i>					
Diabetes, on insulin	11	-0.44	0.55	-0.06	0.72
Diabetes, on other diabetes drug	39	-0.58	1.22	-0.65	1.22
Diabetes, no drug	71	-0.12	0.98	-0.11	1.15
No diabetes	869	0.04	0.99	0.04	0.97

NOTE: SD = standard deviation.

References

1. Deary IJ, Johnson W. Intelligence and education: causal perceptions drive analytic processes and therefore conclusions. *Int J Epidemiol* 2010;39:1362–9.
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3. Ryan CM, Freed MI, Rood JA, Cobitz AR, Waterhouse BR, Strachan MWJ. Improving metabolic control leads to better working memory in adults with type 2 diabetes. *Diabetes Care* 2006;29:345–51.